Risk Factors for Anterior Cruciate Ligament Injury: A Review of the Literature—Part 2: Hormonal, Genetic, Cognitive Function, Previous Injury, and Extrinsic Risk Factors

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HC, Vacek PM, Johnson RJ, Slauterbeck JR, Hashemi J, Shultz SJ, Beynnon BD. Risk Factors for Anterior Cruciate Ligament Injury: A Review of the Literature: Part 2: Hormonal, Genetic, Cognitive Function, Previous Injury and Extrinsic Risk Factors. *Sports Health: A Multidisciplinary Approach* 2012;4(2):155-161.

Made available courtesy of SAGE Publications: http://dx.doi.org/10.1177/1941738111428282.

Abstract:

Context: Injuries to the anterior cruciate ligament (ACL) are immediately disabling and are associated with long-term consequences, such as posttraumatic osteoarthritis. It is important to have a comprehensive understanding of all possible risk factors for ACL injury to identify individuals who are at risk for future injuries and to provide an appropriate level of counseling and programs for prevention.
Objective: This review, part 2 of a 2-part series, highlights what is known and still unknown regarding hormonal, genetic, cognitive function, previous injury, and extrinsic risk factors for ACL injury.
Data Sources: Studies were identified from MEDLINE (1951–March 2011) using the MeSH terms *anterior cruciate ligament*, *knee injury*, and *risk factors*. The bibliographies of relevant articles and reviews were cross-referenced to complete the search.
Study Selection: Prognostic case-control and prospective cohort study designs to evaluate risk factors for ACL injury were included in this review.
Results: A total of 50 case-control and prospective cohort articles were included in parts 1 and 2. Twenty-one focused on hormonal, genetic, cognitive function, previous injury, and extrinsic risk factors.
Conclusions: Several risk factors are associated with increased risk of suffering ACL injury—such as female sex, prior reconstruction of the ACL, and familial predisposition. These risk factors most likely act in combination with the anatomic factors reviewed in part 1 of this series to influence the risk of suffering ACL injury.

Keywords: anterior cruciate ligament (ACL) | knee injury | risk factors

Article:

Injuries to the anterior cruciate ligament (ACL) of the knee are common in athletes and have serious sequelae, including increased risk of early-onset posttraumatic osteoarthritis regardless of the treatment administered.16 Injury rates as high as 2.8 and 3.2 injuries per 10 000 athlete exposures have been reported in women's collegiate sports.17 The identification of factors associated with increased risk of suffering ACL injury during sport and physical activity has become a focus of musculoskeletal research, with the goal of identifying those who are at increased risk of ACL injury so that an intervention can be targeted at them.

This review constitutes the second of a 2-part series. As in part 1, prognostic studies were included on the basis of prospective and case-control designs from peer-reviewed journals. A MEDLINE electronic database search (1951–March 2011) was conducted, as well as cross-referencing of the relevant literature. This yielded a total of 50 articles for inclusion in parts 1 and 2 of this review, 21 of which focused on hormonal, genetic, cognitive function, previous injury, and extrinsic risk factors. Abstracts, case-series studies, and descriptive studies were not included.

Intrinsic Risk Factors

Sex Differences in Baseline Risk

Female athletes have been identified at increased risk of injuring their ACL during certain sports, with reported injury rates that are 3.5 times greater for basketball and 2.67 times greater for soccer when compared with male athletes who participate in these sports at similar levels of play.[29] Very little is known regarding the mechanisms and risk factors that explain this sex discrepancy on the incidence of ACL injury. To date, many studies have focused on identifying differences in potential risk factors for ACL tears in female versus male athletes. Sex-based anatomic differences, neuromuscular control variations, and the effect of sex hormones have been studied.[40] Compared with male athletes, female athletes display different movement and muscle activation patterns[9] and have smaller ACLs with decreased stiffness values and different bony knee geometry.[2,7,8] Females also display greater knee laxity values in comparison with males.[32-34] Understanding the implications of differences for ACL injury risk is difficult because if females have different baseline values of potential risk factors for ACL injury than males, their effects will be confounded with those of sex. Combining data from males and females could therefore obscure the effects of some risk factors or, alternatively, find associations with injury for some risk factors simply because they differ between males and females. Likewise, this concern may apply to combining data from sources, such as age groups, levels of play, ethnic backgrounds, and sports. Although very important, these sources of potential confounding variables have received little attention in the literature.

Hormonal Risk Factors

Female sex hormone concentrations change over the course of the menstrual cycle, and the pattern of change may not be consistent from cycle to cycle. One rationale for studying sex hormones is based on the research that has identified estrogen and progesterone receptor sites on the ACL, and this has introduced the hypothesis that female sex hormones have an effect on the metabolism (synthesis and cleavage of matrix components), composition, and biomechanical properties of the ACL.[15,41] However, there are no case-control or cohort studies in humans that have confirmed that either the presence of these receptor sites on the ACL or the concentrations of sex hormones themselves have an influence on the structural and mechanical properties of ligaments. Most of what is known has been derived from studies performed with the use of animal models.

Studies have been carried out to understand the relationship between variations in sex hormones and risk of suffering ACL injury; however, a dilemma exists in attempting to compare the findings from these studies because many approaches have been used to categorize the phases of the menstrual cycle as a means of quantifying acute hormone concentrations. These differences in cycle phase categorizations and measurement techniques make comparisons between studies very difficult. We identified 5 case-control studies that examined the relationship between menstrual cycle phase and the risk of suffering ACL injury (Table 1).[6,18,19,31,35] Although not included in this review, other studies have attempted to characterize the effects of female sex hormones through descriptive or case-series study designs.[1,3,4,38,39] These studies have reported an increase in the risk of suffering an ACL tear during the preovulatory phase,[6,31] follicular phase,[35] and menstrual phase.[18] One study has identified an increased incidence of injury during the late luteal (postovulatory) phase of the menstrual cycle.[19] Several reviews and consensus statements have attempted to combine results and establish a common cycle phase during which females are at the greatest risk of suffering an ACL injury.

Table 1. Hormonal risk factors.

Author	Study Design	No.	No. of Injured Cases	Significant Risk Factors
Myklebust[19]	Prospective cohort	23	17	Late luteal phase of menstrual cycle
Slauterbeck[35]	Unmatched case-control	38	37	Follicular phase of menstrual cycle
Myklebust[18]	Prospective cohort	69	46	Menstrual phase of menstrual cycle
Beynnon[6]	Matched case-control	91	46	Preovulatory phase of menstrual cycle
Ruedl[31]	Matched case-control	186	93	Preovulatory phase of menstrual cycle

For example, the consensus statement that resulted from the Hunt Valley II meeting in 2005 was that there is evidence in support of the highest incidence of injury occurring in the early and late follicular phases of the menstrual cycle.[11] However, based on the evidence from recent case-control studies that focused on the relationship between the risk of ACL injury and menstrual cycle phase, the literature does not support this statement. Potential weaknesses common to all 5 case-control studies center on the ability of the investigators to accurately identify the cycle phase at the time that the injury occurred. Only 2 of the 5 studies obtained biological samples to measure hormone levels in combination with menstrual cycle history data to identify the phase of menstrual cycle at the time of injury.[6,35] Our review did not identify a validated outcome measure that can use serum, urine, or salivary hormone (progesterone) concentration data alone or in combination with menstrual cycle history data obtained from case-control studies to accurately predict cycle phase at the time of injury in athletic females. In short, investigators cannot assume that study participants (ie, experimental and controls) are within a normal ovulatory cycle that has well-characterized hormonal profiles. While the use of a prospective study design that obtains serum measurements for a full cycle before and after an injury would be the most accurate approach to identify the menstrual cycle phase and hormone concentrations for all individuals at risk for injury, this would require obtaining samples every day for the length of the study from the entire population that is at risk for injury. Because a very large cohort would be needed to generate a meaningful number of ACL injuries, this approach is not practical. While review articles and consensus statements continue to report an increased risk of suffering an ACL injury during the preovulatory phase of the menstrual cycle,[30,34] these findings must be considered with caution until we can accurately determine menstrual status at the time of injury. More research is needed to develop a validated measure that can be used to characterize menstrual cycle phase status at the time of trauma and apply it to studies designed to determine if links exist between cycle phase, acute dosing of sex hormones, and risk of suffering ACL injury.

Genetic Risk Factors

There are currently 2 case-control studies that attempt to assess whether there is a familial predisposition to noncontact ACL tears (Table 2).[10,12] The first study employed a matched case-control design and used a medical history questionnaire to determine the knee ligament injuries of the patients' primary family members.[12] There was a higher incidence rate of ACL injury in the immediate family of the injured group (35%) than that of the control group (4%). In a matched case-control study by Flynn et al, patients with ACL tears were twice as likely to have a relative (first, second, or third degree) with an ACL tear compared with controls without an ACL tear.[10]

Table 2. Genetic risk factors.

Author	Study Design	No.	No. of Injured Cases	Significant Risk Factors
Harner[12]	Matched case-control	54	31	Family history of anterior cruciate ligament tear
Flynn[10]	Matched case-control	342	171	Family history of anterior cruciate ligament tear
Posthumus[27]	Case-control	247	117	Underrepresentation of *COL1A1* genotype in injured group
Posthumus[28]	Case-control	345	129	Underrepresentation of *COL5A1* sequence variants in injured females
Posthumus[26]	Case-control	345	129	Overrepresentation of *COL12A1* sequence variants in injured females
Posthumus[25]	Case-control	345	129	Gene variants on the 11q22 chromosome

One group has published 4 articles that identify 3 genetic factors associated with ACL tears (Table 2).[25-28] These studies were based on unmatched case-control designs and were performed in a white South African population. A rare TT genotype of the COL1A1 Sp1 binding site polymorphism was underrepresented in those with ACL injuries in comparison with the controls.[26] The COL1A1 gene encodes a protein chain within type I collagen, a major structural component of ligaments. ACL-injured patients were 4 times more likely to have a family member with a ligament injury of any kind in comparison with controls.[26] Likewise, the CC genotype of a variant in the COL5A1 gene has been associated with ACL tears in females.[28] The COL5A1 gene codes for a protein chain in type V collagen, found in ligaments and tendons.[28] Third, these investigators found that the AA genotype of the COL12A1 AluI polymorphism is overrepresented in female ACL injured patients.[27] This gene encodes for protein chains in type XII collagen, which is believed to regulate fibril diameter in ligaments.[27] The most recent article reported an association between the chromosomal region 11q22 and risk of ACL tear.[25] Several matrix metalloproteinase genes, including those that are physiologic mediators of collagen cleavage and removal, are located on chromosome 11q22. In this group of ACL-injured patients, AG and GG genotypes of 1 matrix metalloproteinase variant were significantly underrepresented compared with uninjured patients.[25] The frequency of haplotypes of the variants within the gene were significantly different between injured and uninjured groups.[25] It is important that genetic variants be assessed in different populations at risk of suffering ACL injury and that their associated phenotypes be identified.

Cognitive Function Risk Factors

A proposed risk factor that deserves further investigation is neurocognitive function (Table 3). A nested case-control study prospectively collected data based on Immediate Post-concussion Assessment and Cognitive Testing to determine if there were baseline differences between athletes who went on to tear their ACL and matched controls.[36] This assessment is a neurocognitive test battery designed to assess function before and after concussion. ACL-injured patients had significantly slower reaction time as well as slower processing speed. Compared with matched controls, those with ACL injury also displayed significantly lower scores on visual and verbal memory sections and a lower total score.36 More research is needed in this area to determine if neurocognitive process or behavior is predictive of increased risk of ACL injury.

Table 3. Cognitive function risk factors.

Author	Study Design	No.	No. of Injured Patients	Significant Risk Factors
Swanik[36]	Matched case-control	160	80	Slower reaction time, slower processing speed, lower visual and verbal memory scores

Previous Injury

Previous ACL reconstruction is a risk factor for ACL injury in several prospective studies, both in the contralateral knee and for reinjury of the ACL graft (Table 4).[21,37] One group performed a prospective study of elite soccer players to determine if ACL reconstruction is a significant predictor for repeated injury to ACL graft or injury to the contralateral knee.[37] Players with a history of ACL reconstruction had a higher incidence of new knee injuries of any type compared with players without a history of ACL injury.[37] Orchard et al found that previous ACL reconstruction is a significant risk factor for subsequent noncontact ACL injury, for both the reconstructed and the contralateral knee.[21] Patients with prior ACL injury within the previous 12 months were 11.3 times more likely to injure their graft or contralateral ACL than those who were uninjured. Likewise, those with an ACL injury prior to the previous 12 months were 4.4 times more likely to injure the graft or contralateral ACL than those who were uninjured.[21] Researchers have also shown that previous ankle injury is related to ACL injury in athletes.[13] Those with a history of ACL injury were more likely to have a prior ipsilateral ankle sprain compared with those who had no history of ankle sprain.[13]

Table 4. Previous injury.

Author	Study Design	No.	No. of Injured Patients	Significant Risk Factors
Walden[37]	Prospective cohort	310	24	History of anterior cruciate ligament reconstruction
Orchard[21]	Prospective cohort	1643	63	History of anterior cruciate ligament reconstruction
Kramer[13]	Case-control	66	33	Prior ipsilateral ankle injury

Location of injury (knee, lower extremity, trunk), type of injury (isolated ligament vs combined ligament and articular structures), and magnitude of injury (degree of ligament sprain) are important factors to consider. Also, it is very important to evaluate the type of recovery attained through rehabilitation (restoration of joint biomechanics, strength, proprioception, and neuromuscular control) when a patient is returning to preinjury activity. These probably combine to influence the risk of reinjury to the graft or injury to the other knee and should be carefully considered in future studies.

Extrinsic Risk Factors

Extrinsic risk factors include weather, type and condition of playing surface, and footwear (Table 5). These factors influence the shoe-surface interaction, which is most likely a relevant risk factor.[14,20,21-24] Weather conditions have been related to an increased risk of ACL injury. For example, wet and rainy weather may reduce the friction between the athlete’s shoe and playing surface.[22,24] A high level of friction and mechanical interlock between the shoe and the playing surface may be produced by many sources: the type and number of cleats, the design of the shoe itself, the type of grass, artificial grass or floor surface, and the weather.[24]

Table 5. Extrinsic risk factors.

Author	Study Design	No.	No. of Injured Cases	Significant Risk Factors
Lambson[14]	Prospective cohort	3119 athletes	42	Cleats with higher torsional resistance (edge design)
Orchard[22]	Prospective cohort	2280 matches	59	High evaporation, low rainfall before match
Orchard[21]	Prospective cohort	1643 athletes	63	High evaporation, low rainfall before match
Orchard[24]	Prospective cohort	5910 games	252	Hot weather in open stadiums
Orchard[23]	Prospective cohort	3635 matches	88	Bermuda grass fields (more "trapping" of the cleat)
Olsen[20]	Prospective cohort	6724 matches	53	Synthetic floors for females

In American football specifically, cleat design influences the torsional resistance between the foot and the ground, and the type of cleats affects ACL injury risk.14 Specifically, in a prospective cohort study, Lambson et al showed that certain types of cleats produced significantly higher levels of torsional resistance on the same surface. The cleat with the highest torsional resistance (edge cleats) had longer irregular cleats placed at the periphery of the sole with a number of smaller pointed cleats positioned centrally. This cleat design was associated with a significantly higher ACL injury rate on various playing surfaces in comparison with the other designs, including systems with smaller and flatter cleats, fewer cleats, or rotating cleats.[14]

Orchard et al performed 4 prospective studies designed to evaluate the effect of weather and playing surface condition on ACL injury risk, as well as knee injury risk overall.[22-24] The first 2 studies revealed that high evaporation rates in the month before the match (relative risk = 2.8 and 2.55) as well as low rainfall in the year before the match (relative risk = 1.93 and 2.87) were associated with increased ACL tear rates in the Australian Football League.[21,22] There was an increased risk of ACL injury in hot weather in open stadiums versus cooler weather.[24] The most recent study by Orchard et al assessed the contribution of ground variables such as grass type to the rate of ACL tears in Australian football.[23] Rye grass stadiums were associated with fewer ACL injuries. When variables were analyzed in a multivariable model, ACL injury risk increased with higher level of play, northern venues, more evaporation, early season games, and stadiums using Bermuda grass turf. The authors hypothesized that less "trapping" of the cleat occurred on rye grass than Bermuda grass based on the amount of thatch.[23] This study did not, however, account for differences among types of cleats.

Olsen et al prospectively studied elite Norwegian handball players to determine if ACL injury rate was affected by wooden versus synthetic indoor floors. The risk of ACL injury was 2.35 times higher on synthetic floors for female athletes.[20]

The extrinsic risk factors associated with injury suggests that there may be some interaction between the footware and playing surface for activities that take place indoors and that the same extrinsic factors in combination with weather interact for outdoor activities. More work is needed to know if the frictional coefficients and mechanical interlock between various shoes and playing surfaces are related to the risk of suffering ACL injury to determine if thresholds exist below which injury risk is reduced.

Conclusion

Several risk factors are associated with ACL injury. Females are at increased risk for suffering an ACL injury compared with males when taking part in the same sports at similar levels of exposure.[29] Several investigations have focused on whether the risk of suffering ACL injury changes over the course of the menstrual cycle or remains constant over time. We were unable to establish a consensus because many study designs, menstrual cycle classification schemes, and analysis techniques have been used. Even more important, we were unable to identify a validated, standardized technique that accurately stages the menstrual cycle at the time of injury in active individuals.

As shown in part 1 of this review, it is very likely that multiple risk factors act in combination to influence the risk of ACL injury.[5] Future studies should focus on examining many, if not all, known or possible intrinsic and extrinsic risk factors for ACL injury in prospective cohort or case-control studies to expand our knowledge of ACL injury risk.

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